REMARKS

Claim 19 has been amended. The instant amendment finds support throughout the specification and the claims as originally filed. As such, no new matter has been added.

Rejection of Claims 1-7, 10, 13, and 16 Under 35 U.S.C. § 102

The Examiner has rejected Claims 1-7, 10, 13, and 16 under 35 U.S.C. § 102(b) as allegedly being anticipated by van Erp et al., (van Erp). Applicants respectfully disagree.

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). Applicant respectfully submits that van Erp does not teach each and every element of the claimed invention.

van Erp fails to teach pH adjustments of a cell line to activate endogenous proteases to produce antigen-binding antibody fragments. van Erp discloses the presence of proteolytic enzymes in hybridoma cell lines capable of antibody degradation and further discloses the purification of such proteases from the hybridoma cell lines. These proteases are then added to purified antibody samples, yielding fragments of particular size (110K, 47K, and 25K). The authors postulate that the 110K fragment yielded by the proteolysis most likely corresponds to an $F(ab')_2$ fragment.

However, the van Erp reference fails to teach "adjusting pH conditions of the cell media" to activate endogenous enzymes in the cell media to effect antibody cleavage, as recited in both independent claims of the instant application. van Erp's disclosure is limited to pH adjustment of supernatant, and not cell media as recited in the claims. In addition, van Erp does not teach nor suggest "incubating said cell line under the adjusted pH conditions", as recited in Claim 1. van Erp only teaches adjusting the pH of supernatant that does not contain any cells. Additionally, *Kratje* et al., cited by the Examiner, states that "cultures with serum-free medium proteases can have a negative influence upon cell proliferation as well as causing protein substrate loss." Accordingly, the references cited by the Examiner teach that it is undesirable to adjust pH of cell media to activate at least one endogenous enzyme and then incubate a cell line under the adjusted pH conditions so that antibodies are cleared into antigen biding fragments as claimed.

In addition, Claims 1 and 19 recite that the antibody fragments produced are "antigen binding fragments". Although, van Erp teaches that antibody degradation by the specific proteases results in 110K fragments, there is no teaching or disclosure that the fragments produced are capable of binding an antigen. There are no experiments, qualitative analyses, or even postulations that the fragments produced retain their ability to bind antigen, as recited in Claims 1 and 19.

For all the above reasons, Applicant respectfully submits that van Erp et al., do not teach each and every element of the claimed invention. Applicants respectfully request withdrawal of the Examiner's rejection of Claims 1-7, 10, 13, and 16 of the instant application under 35 U.S.C. § 102(b) as allegedly being anticipated by van Erp et al., and respectfully submit that the application is in condition for allowance.

Rejection of Claims 1, 8, 9, 11, 14, 15, 17, 18, 19, 20-23 and 25 Under 35 U.S.C. § 103

The Examiner has rejected Claims 1, 8, 9, 11, 17, 18, 19, 21-23 and 25 of the instant application under 35 U.S.C. § 103(a) as being unpatentable over van Erp, in view of Kratje et al., (Kratje) and Mason et al., (Mason).

To establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). As discussed above, van Erp fails to teach pH adjustments of a cell line to activate endogenous proteases to produce antigen-binding antibody fragments, as disclosed by independent Claims 1 and 19 of the instant application. The deficiencies of van Erp are not cured by either Kratje or Mason.

As dependent Claims, by definition, include the limitations of their respective independent claim, a finding of non-obviousness for the independent claims in the instant application necessitates a finding of non-obviousness for the dependent claims as well. Kratje discloses the proteolytic capacities of the proteases secreted in culture supernatants but fails to teach or disclose the generation of antigen-binding fragments of an antibody from an antibody-producing cell-line growing in a cell media under conditions to express antibodies by adjusting the pH conditions of the cell media, as disclosed by independent Claims 1 and 19. Further, Kratje does not teach that the activity of proteases endogenously present in hybridoma cell lines are pH dependent:

> [t]he proteolytic activity of hybridoma cells were not pH dependent (Fig8). ... This result was different to that obtained from investigations of other mouse hybridoma cells (Schlaeger et al., 1987) where a pH dependence of the proteolytic activity was found in the culture supernatant. However, Schlaeger and co-workers used serum-containing medium for their pH-dependency analysis in contrast to the serum-free conditions in our analysis.

(120, col. 2, ¶1). As such, Kratje not only fails to disclose elements of the claims not disclosed by van Erp but teaches away from "incubating said cell line under the adjusted pH conditions", as recited in Claim 1. Additionally, Mason fails to fill the void in disclosure left by van Erp and Kratje. As the references cited by the Examiner do not teach each and every limitation of the rejected claims, Applicant respectfully requests the withdrawal of the Examiner's rejection of Claims 1, 8, 9, 11, 17-19, 21-23, and 25 as obvious under 35 U.S.C. §103(a) over van Erp in view of Kratje, and further in view of Mason.

Also, the Examiner has rejected Claims 1, 14, 15, 19 and 20 under 35 U.S.C. §103(a) as being unpatentable over van Erp in view of Kratje, and further in view of Zhang et al., (Zhang) and Schiefferli et al., (Schifferli). Neither Zhang nor Schifferli complete the gaps in disclosure left by van Erp and Kratje. As such, the Examiner has not fulfilled his burden of presenting a *prima facie* case that Claims 1, 14, 15, 19 and 20 are obvious under 35 U.S.C. §103(a) over van Erp in view of Kratje, and further in view of Zhang and Schifferli.

For all the above reasons, Applicant respectfully submits that the references cited by the Examiner do not teach each and every element of the claimed invention. Applicants respectfully request withdrawal of the Examiner's rejection of Claims 1, 8, 9, 11, 13, 16-19, 21-23, and 25 of the instant application under 35 U.S.C. § 103(a) and respectfully submit that the application is in condition for allowance.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present

disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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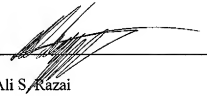
By: 

Ali S. Razai
Registration No. 60,771
Attorney of Record
Customer No. 20,995
(619) 235-8550

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